GCCGCCGCGCGCCATGGAGCCCGAGTGAGCGCGCGCGCCGCCG GACGACATGGAAACGGCGCCGACCCGGGCCCCTCCGCCGCCGCCGCCGCCGC GCTGCTGCTGCTGCTACTGCAGCTTGGTCCCCGCCGCGGCCTCACCGCTCC TGTTGTTTGCCAACCGCCGGGATGTGCGGCTAGTGGATGCCGGCGGAGTGAAG CTGGAGTCCACCATTGTGGCCAGTGGCCTGGAGGATGCAGCTGCTGTAGACTT CCAGTTCTCCAAGGGTGCTGTGTACTGGACAGATGTGAGCGAGGAGGCCATCA AACAGACCTACCTGAACCAGACTGGAGCTGCTGCACAGAACATTGTCATCTCG GGCCTCGTGTCACCTGATGGCCTGGCCTGTGACTGGGTTGGCAAGAAGCTGTA CTGGACGGACTCCGAGACCAACCGCATTGAGGTTGCCAACCTCAATGGGACGT CCCGTAAGGTTCTCTTCTGGCAGGACCTGGACCAGCCAAGGGCCATTGCCCTG GATCCTGCACATGGGTACATGTACTGGACTGACTGGGGGGGAAGCACCCCGGAT CGAGCGGCAGGATGGATGGCAGTACCCGGAAGATCATTGTAGACTCCGACA TTTACTGGCCCAATGGGCTGACCATCGACCTGGAGGAACAGAAGCTGTACTGG GCCGATGCCAAGCTCAGCTTCATCCACCGTGCCAACCTGGACGGCTCCTTCCG GCAGAAGGTGGTGGAGGCCAGCCTCACTCACCCTTTTGCCCTGACACTCTCTG AAGTGGACAGGGAGCAGAGGAAGGAGATCCTTAGTGCTCTGTACTCACCCAT GGACATCCAAGTGCTGAGCCAGGAGCGGCAGCCTCCCTTCCACACACCATGCG AGGAGGACAACGGTGGCTGTTCCCACCTGTGCCTGTCCCCGAGGGAGCCT TTCTACTCCTGTGCCTGCCCCACTGGTGTGCAGTTGCAGGACAATGGCAAGAC GTGCAAGACAGGGGCTGAGGAAGTGCTGCTGGCTCGGAGGACAGACCTGA GGAGGATCTCTCTGGACACCCCTGACTTCACAGACATAGTGCTGCAGGTGGGC GACATCCGGCATGCCATTGCCATTGACTACGATCCCCTGGAGGGCTACGTGTA $\tt CTGGACCGATGATGAGGTGCGGGCTATCCGCAGGGCGTACCTAGATGGCTCAG$ GTGCGCAGACACTGTGAACACTGAGATCAATGACCCCGATGGCATTGCTGTG GACTGGGTCGCCCGGAACCTCTACTGGACAGATACAGGCACTGACAGAATTGA GGTGACTCGCCTCAACGGCACCTCCCGAAAGATCCTGGTATCTGAGGACCTGG ACGAACCGCGAGCCATTGTGTTGCACCCTGTGATGGGCCTCATGTACTGGACA GACTGGGGGGAGAACCCCAAAATCGAATGCGCCAACCTAGATGGGAGAGATCG GCATGTCCTGGTGAACACCTCCCTTGGGTGGCCCAATGGACTGGCCCTGGACC TGCAGGAGGCCAAGCTGTACTGGGGGGGATGCCAAAACTGATAAAATCGAGGTG ATCAACATAGACGGGACAAAGCGGAAGACCCTGCTTGAGGACAAGCTCCCACA CATTTTTGGGTTCACACTGCTGGGGGGACTTCATCTACTGGACCGACTGGCAGA GACGCAGTATTGAAAGGGTCCACAAGGTCAAGGCCAGCCGGGATGTCATCATT GATCAACTCCCCGACCTGATGGGACTCAAAGCCGTGAATGTGGCCAAGGTTGT CGGAACCAACCCATGTGCGGATGGAAATGGAGGGTGCAGCCATCTGTGCTTCT TCACCCCACGTGCCACCAAGTGTGGCCTGCCCCATTGGCCTGGAGCTGTTGAGT GACATGAAGACCTGCATAATCCCCGAGGCCTTCCTGGTATTCACCAGCAGAGC CACCATCCACAGGATCTCCCTGGAGACTAACAACAACGATGTGGCTATCCCAC TCACGGGTGTCAAAGAGGCCTCTGCACTGGACTTTGATGTGTCCAACAATCAC

219

ATCTACTGGACTGATGTTAGCCTCAAGACGATCAGCCGAGCCTTCATGAATGG GAGCTCAGTGGAGCACGTGATTGAGTTTGGCCTCGACTACCCTGAAGGAATGG CTGTGGACTGGATGGGCAAGAACCTCTATTGGGCGGACACAGGGACCAACAGG ATTGAGGTGGCCCGGCTGGATGGGCAGTTCCGGCAGGTGCTTGTGTGGAGAGA CCTTGACAACCCCAGGTCTCTGGCTCTGGATCCTACTAAAGGCTACATCTACT AATTGTATGACACTGGTAGACAAGGTGGGCCGGGCCAACGACCTCACCATTGA TTATGCCGACCAGCGACTGTACTGGACTGACCTGGACACCAACATGATTGAGT CTTCCAACATGCTGGGTCAGGAGCGCATGGTGATAGCTGACGATCTGCCCTAC GCATAGCATTGAACGGGCGGACAAGACCAGTGGGCGGAACCGCACCCTCATCC AGGGTCACCTGGACTTCGTCATGGACATCCTGGTGTTCCACTCCTCCCGTCAG GATGGCCTCAACGACTGCGTGCACAGCAATGGCCAGTGTGGGCAGCTGTGCCT CGCCATCCCGGAGGCCACCGCTGTGGCTGTGCTTCACACTACACGCTGGACC CCAGCAGCCGCAACTGCAGCCCGCCCTCCACCTTCTTGCTGTTCAGCCAGAAA TTTGCCATCAGCCGGATGATCCCCGATGACCAGCTCAGCCCGGACCTTGTCCT ACCCCTTCATGGGCTGAGGAACGTCAAAGCCATCAACTATGACCCGCTGGACA AGTTCATCTACTGGGTGGACGGCCCAGAACATCAAGAGGGCCAAGGACGAC GGTACCCAGCCTCCATGCTGACCTCTCCCAGCCAAAGCCTGAGCCCAGACAG ACAGCCACACGACCTCAGCATTGACATCTACAGCCGGACACTGTTCTGGACCT GTGAGGCCACCAACACTATCAATGTCCACCGGCTGGATGGGGATGCCATGGGA GTGGTGCTTCGAGGGGACCGTGACAAGCCAAGGGCCATTGCTGTCAATGCTGA GCGAGGGTACATGTACTTTACCAACATGCAGGACCATGCTGCCAAGATCGAGC GAGCCTCCCTGGATGGCACAGAGCGGGAGGTCCTCTTCACCACAGGCCTCATC CGTCCCGTGGCCCTTGTGGTGGACAATGCTCTGGGCAAGCTCTTCTGGGTGGA TGCCGACCTAAAGCGAATCGAAAGCTGTGACCTCTCTGGGGCCAACCGCCTGA CCCTGGAAGATGCCAACATCGTACAGCCAGTAGGTCTGACAGTGCTGGGCAGG CACCTCTACTGGATCGACCGCCAGCAGCAGATGATCGAGCGCGTGGAGAAGAC TCCATGCCGTGGAGGAGTCAGCCTGGAGGAGTTCTCAGCCCATCCTTGTGCC CGAGACAATGGCGGCTGCTCCCACATCTGTATCGCCAAGGGTGATGGAACACC GCGCTGCTCGTGCCCTGTCCACCTGGTGCTCCTGCAGAACCTGCTGACTTGTG GTGAGCCTCCTACCTGCTCCCCTGATCAGTTTGCATGTACCACTGGTGAGATC GACTGCATCCCCGGAGCCTGGCGCTGTGACGGCTTCCCTGAGTGTGCTGACCA GAGTGATGAAGAAGGCTGCCCAGTGTGCTCCGCCTCTCAGTTCCCCTGCGCTC GAGGCCAGTGTGTGGACCTGCGGTTACGCTGCGACGGTGAGGCCGACTGCCAG GATCGCTCTGATGAAGCTAACTGCGATGCTGTCTGTCTGCCCAATCAGTTCCG GTGCACCAGCGGCCAGTGTGTCCTCATCAAGCAACAGTGTGACTCCTTCCCCG ACTGTGCTGATGGGTCTGATGAGCTCATGTGTGAAATCAACAAGCCACCCTCT GATGACATCCCAGCCCACAGCAGTGCCATTGGGCCCGTCATTGGTATCATCCT CTCCCTCTTCGTCATGGGCGGGGTCTACTTTGTCTGCCAGCGTGTGATGTGCC

FIGURE 1C

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METAPTRAPPPPPPPLLLLVLYCSLVPAAASPLLLFANRRDVRLVDAGGVKLE STIVASGLEDAAAVDFQFSKGAVYWTDVSEEAIKQTYLNQTGAAAQNIVISGL VSPDGLACDWVGKKLYWTDSETNRIEVANLNGTSRKVLFWQDLDOPRAIALDP AHGYMYWTDWGEAPRIERAGMDGSTRKIIVDSDIYWPNGLTIDLEEQKLYWAD AKLSFIHRANLDGSFROKVVEGSLTHPFALTLSGDTLYWTDWOTRSIHACNKW TGEORKEILSALYSPMDIQVLSQERQPPFHTPCEEDNGGCSHLCLLSPREPFY SCACPTGVOLODNGKTCKTGAEEVLLLARRTDLRRISLDTPDFTDIVLOVGDI RHAIAIDYDPLEGYVYWTDDEVRAIRRAYLDGSGAOTLVNTEINDPDGIAVDW VARNLYWTDTGTDRIEVTRLNGTSRKILVSEDLDEPRAIVLHPVMGLMYWTDW GENPKIECANLDGRDRHVLVNTSLGWPNGLALDLQEGKLYWGDAKTDKIEVIN IDGTKRKTLLEDKLPHIFGFTLLGDFIYWTDWQRRSIERVHKVKASRDVIIDO LPDLMGLKAVNVAKVVGTNPCADGNGGCSHLCFFTPRATKCGCPIGLELLSDM KTCIIPEAFLVFTSRATIHRISLETNNNDVAIPLTGVKEASALDFDVSNNHIY WTDVSLKTISRAFMNGSSVEHVIEFGLDYPEGMAVDWMGKNLYWADTGTNRIE VARLDGOFROVLVWRDLDNPRSLALDPTKGYIYWTEWGGKPRIVRAFMDGTNC MTLVDKVGRANDLTIDYADQRLYWTDLDTNMIESSNMLGQERMVIADDLPYPF GLTOYSDYIYWTDWNLHSIERADKTSGRNRTLIQGHLDFVMDILVFHSSRODG LNDCVHSNGQCGQLCLAIPGGHRCGCASHYTLDPSSRNCSPPSTFLLFSOKFA ISRMIPDDQLSPDLVLPLHGLRNVKAINYDPLDKFIYWVDGRQNIKRAKDDGT OPSMLTSPSQSLSPDRQPHDLSIDIYSRTLFWTCEATNTINVHRLDGDAMGVV LRGDRDKPRAIAVNAERGYMYFTNMQDHAAKIERASLDGTEREVLFTTGLIRP VALVVDNALGKLFWVDADLKRIESCDLSGANRLTLEDANIVQPVGLTVLGRHL YWIDRQQQMIERVEKTTGDKRTRVQGRVTHLTGIHAVEEVSLEEFSAHPCARD NGGCSHICIAKGDGTPRCSCPVHLVLLONLLTCGEPPTCSPDOFACTTGEIDC IPGAWRCDGFPECADQSDEEGCPVCSASQFPCARGOCVDLRLRCDGEADCODR SDEANCDAVCLPNQFRCTSGQCVLIKQQCDSFPDCADGSDELMCEINKPPSDD IPAHSSAIGPVIGIILSLFVMGGVYFVCQRVMCQRYTGASGPFPHEYVGGAPH VPLNFIAPGGSOHGPFPGIPCSKSVMSSMSLVGGRGSVPLYDRNHVTGASSSS SSSTKATLYPPILNPPPSPATDPSLYNVDVFYSSGIPATARPYRPYVIRGMAP PTTPCSTDVCDSDYSISRWKSSKYYLDLNSDSDPYPPPPTPHSQYLSAEDSCP PSPGTERSYCHLFPPPPSPCTDSS (SEO ID NO: 8)

2

FIGURE 2

Construct

Gene:

193

Gi Number(s): 6678715

Gene Family:

EGF domain protein

Gene

Subfamily:

Low-density lipoprotein receptor

Gene Sequence: full-length cDNA, Mouse

underlined = deleted in targeting construct

[] = sequence flanking Neo insert in targeting construct

GCCGCGGCGCCCGAGGCGGGGGCAAGAGGCGCCGGGAGGCCCGCGAGGATCCACCGCCGCCG CAGCTTGGTCCCCGCCGCGCCTCACCGCTCCTGTTGTTTGCCAACCGCCGGGATGTGCG GCTAGTGGATGCCGGCGGAGTGAAGCTGGAGTCCACCATTGTGGCCAGTGGCCTGGAGGA TGCAGCTGCTGTAGACTTCCAGTTCTCCAAGGGTGCTGTGTACTGGACAGATGTGAGCGA GGAGGCCATCAAACAGACCTACCTGAACCAGACTGGAGCTGCTGCACAGAACATTGTCAT $\tt CTCGGGCCTCGTGTCACCTGATGGCCTGGCCTGTGACTGGGTTGGCAAGAAGCTGTACTG$ GACGGACTCCGAGACCAACCGCATTGAGGTTGCCAACCTCAATGGGACGTCCCGTAAGGT TCTCTTCTGGCAGGACCTGGACCAGCCAAGGGCCATTGCCCTGGATCCTGCACATGGGTA TACCCGGAAGATCATTGTAGACTCCGACATTTACTGGCCCAATGGGCTGACCATCGACCT GGAGGAACAGAAGCTGTACTGGGCCGATGCCAAGCTCAGCTTCATCCACCGTGCCAACCT CAAGTGGACAGGGGAGCAGAGGAAGGAGATCCTTAGTGCTCTGTACTCACCCATGGACAT CCAAGTGCTGAGCCAGGAGCGGCAGCCTCCCTTCCACACACCATGCGAGGAGGACAACGG CACTGGTGTGCAGTTGCAGGACAATGGCAAGACGTGCAAGACAGGGGCTGAGGAAGTGCT GCTGCTGGCTCGGAGGACAGACCTGAGGAGGATCTCTCTGGACACCCCTGACTTCACAGA CATAGTGCTGCAGGTGGGCGACATCCGGCATGCCATTGCCATTGACTACGATCCCCTGGA GGGCTACGTGTACTGGACCGATGATGAGGTGCGGGCTATCCGCAGGGCGTACCTAGATGG CTCAGGTGCGCAGACACTTGTGAACACTGAGATCAATGACCCCGATGGCATTGCTGTGGA CTGGGTCGCCCGGAACCTCTACTGGACAGATACAGGCACTGACAGAATTGAGGTGACTCG CCTCAACGGCACCTCCCGAAAGATCCTGGTATCTGAGGACCTGGACGAACCGCGAGCCAT TGTGTTGCACCCTGTGATGGGCCTCATGTACTGGACAGACTGGGGGGGAGAACCCCAAAAT CGAATGCGCCAACCTAGATGGGAGAGATCGGCATGTCCTGGTGAACACCTCCCTTGGGTG GCCCAATGGACTGGCCCTGGACCTGCAGGAGGGCAAGCTGTACTGGGGGGGATGCCAAAAC TGATAAAATCGAGGTGATCAACATAGACGGGACAAAGCGGAAGACCCTGCTTGAGGACAA GCTCCCACACATTTTTGGGTTCACACTGCTGGGGGACTTCATCTACTGGACCGACTGGCA GAGACGCAGTATTGAAAGGGTCCACAAGGTCAAGGCCAGCCGGGATGTCATCATTGATCA ATGTGCGGATGGAAATGGAGGGTGCAGCCATCTGTGCTTCTTCACCCCACGTGCCACCAA GTGTGGCTGCCCCATTGGCCTGGAGCTGTTGAGTGACATGAAGACCTGCATAATCCCCGA GGCCTTCCTGGTATTCACCAGCAGAGCCACCATCCACAGGATCTCCCTGGAGACTAACAA CAACGATGTGGCTATCCCACTCACGGGTGTCAAAGAGGCCTCTGCACTGGACTTTGATGT GTCCAACAATCACATCTACTGGACTGATGTTAGCCTCAAGACGATCAGCCGAGCCTTCAT GAATGGGAGCTCAGTGGAGCACGTGATTGAGTTTGGCCTCGACTACCCTGAAGGAATGGC TGTGGACTGGATGGGCAAGAACCTCTATTGGGCGGACACAGGGACCAACAGGATTGAGGT GGCCCGGCTGGATGGGCAGTTCCGGCAGGTGCTTGTGTGGAGAGACCTTGACAACCCCAG GTCTCTGGCTCTGGATCCTACTAAAGGCTACATCTACTGGACTGAGTGGGGTGGCAAGCC AAGGATTGTGCGGGCCTTCATGGATGGGACCAATTGTATGACACTGGTAGACAAGGTGGG CCGGGCCAACGACCTCACCATTGATTATGCCGACCAGCGACTGTACTGGACTGACCTGGA

CCTGCATAGCATTGAACGGGCGGACAAGACCAGTGGGCGGAACCGCACCCTCATCCAGGG TCACCTGGACTTCGTCATGGACATCCTGGTGTTCCACTCCTCCCGTCAGGATGGCCTCAA ${\tt CGACTGCGTGCACAGCAATGGCCAGTGTGGGCAGCTGTGCCTCGCCATCCCCGGAGGCCA}$ $\verb|CCGCTGTGGCTGTGCTTCACACTACACGCTGGACCCCAGCAGCCGCAACTGCAGCCCGCC|\\$ CTCCACCTTCTTGCTGTTCAGCCAGAAATTTGCCATCAGCCGGATGATCCCCGATGACCA GCTCAGCCCGGACCTTGTCCTACCCCTTCATGGGCTGAGGAACGTCAAAGCCATCAACTA TGACCCGCTGGACAAGTTCATCTACTGGGTGGACGGGCCCAGAACATCAAGAGGGCCAA GGACGACGGTACCCAGCCTCCATGCTGACCTCTCCCAGCCAAAGCCTGAGCCCAGACAG ACAGCCACACGACCTCAGCATTGACATCTACAGCCGGACACTGTTCTGGACCTGTGAGGC CACCAACACTATCAATGTCCACCGGCTGGATGGGATGCCATGGGAGTGGTGCTTCGAGG GGACCGTGACAAGCCAAGGGCCATTGCTGTCAATGCTGAGCGAGGGTACATGTACTTTAC CAACATGCAGGACCATGCTGCCAAGATCGAGCGAGCCTCCCTGGATGGCACAGAGCGGGA GGTCCTCTTCACCACAGGCCTCATCCGTCCCGTGGCCCTTGTGGTGGACAATGCTCTGGG CAAGCTCTTCTGGGTGGATGCCGACCTAAAGCGAATCGAAAGCTGTGACCTCTCTG [GGG CCAACCGCCTGACCCTGGAAGATGCCAACATCGTACAGCCAGTAGGTCTGACAGTGCTGG GCAGGCACCTCTACTGGATCGACCGCCAGCAGCAGATGATCGAGCGCGTGGAGAAGACC] CGTGGAGGAAGTCAGCCTGGAGGAGTTCT] CAGCCCATCCTTGTGCCCGAGACAATGGCG GCTGCTCCCACATCTGTATCGCCAAGGGTGATGGAACACCGCGCTGCTCGTGCCCTGTCC ACCTGGTGCTCCTGCAGAACCTGCTGACTTGTGGTGAGCCTCCTACCTGCTCCCCTGATC AGTTTGCATGTACCACTGGTGAGATCGACTGCATCCCCGGAGCCTGGCGCTGTGACGGCT TCCCTGAGTGTGCTGACCAGAGTGATGAAGAAGGCTGCCCAGTGTGCTCCGCCTCTCAGT TCCCCTGCGCTCGAGGCCAGTGTGTGGACCTGCGGTTACGCTGCGACGGTGAGGCCGACT GCACCAGCGGCCAGTGTGTCCTCATCAAGCAACAGTGTGACTCCTTCCCCGACTGTGCTG ATGGGTCTGATGAGCTCATGTGTGAAATCAACAAGCCACCCTCTGATGACATCCCAGCCC ACAGCAGTGCCATTGGGCCCGTCATTGGTATCATCCTCTCCCTCTTCGTCATGGGCGGGG TCTACTTTGTCTGCCAGCGTGTGATGTGCCAGCGCTACACAGGGGCCCAGTGGGCCCTTTC $\verb|CCCACGAGTATGTTGGTGGAGCCCCTCATGTGCCTCTCAACTTCATAGCCCCAGGTGGCT|\\$ CACAGCACGGTCCCTTCCCAGGCATCCCGTGCAGCAAGTCCGTGATGAGCTCCATGAGCC CCCCGGCCACAGACCCCTCTCTCTACAACGTGGACGTGTTTTATTCTTCAGGCATCCCGG CCACCGCTAGACCATACAGGCCCTACGTCATTCGAGGTATGGCACCCCCAACAACACCGT GCAGCACAGATGTGTGACAGTGACTACAGCATCAGTCGCTGGAAGAGCAGCAAATACT ACCTATCTGCAGAGGACAGCTGCCCACCCTCACCAGGCACTGAGAGGAGTTACTGCCACC TCTTCCCGCCCCACCGTCCCCTGCACGGACTCGTCCTGACCTCGGCCGTCCACCCGGC CCTGCTGCCTCCCTGTAAATATTTTTAAATATGAACAAAGGAAAAATATATTTTATGATT TAAAAAATAAATATAATTGGGGTTTTTTAACAAGTGAGAAATGTGAGCGGTGAAGGGGTGG GCAGGGCTGGGAAACTTTTCTAG

Gene Sequence
Structure *

Size of full-length
cDNA: 5119 bp

FIGURE 3B

Targeting Vector* (genomic sequence)

Construct Number: 992

Arm Length:

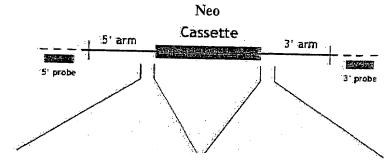
5': 1.5 kb

3': 2.9 kb

Ξ

7

* Not drawn to scale



5'>AAATATGCATTATCCTGAGCA CAGTGGGTCTGGCCCTTCACTTGG CTGCCACTCATGGAGCCTTTATGC TAACCACAGGGGCCAACCGCCTGA CCCTGGAAGATGCCAACATCGTAC AGCCAGTAGGTCTGACAGTGCTGG GCAGCACCTCTACTGGATCGACC GCCAGCAGCAGATGATCGAGCGTG TGGAGAAGACC<3'

(SEQ ID NO: 5)

43

5'>TCACTGGCATCCATGCAGTG:
AGGAAGTCAGCCTGGAGGAGTTCT
GTACGTGAGAGGGGACAGTGTTTG
TGGTGGGGTCTCCTGGGGGAAGGT
GAATCAGCCCTACTGGCATCAGAT
GGGCTGCTGGTGCAAGAGCAGTGT
GCCTGAGGAGCTCATGGCCTCAGC
ACCGAAGGCCAGTGCATGTCCAGA
TGTCTGCCTCT<3'

(SEQ ID NO: 146)

#4

FIGURE 3C

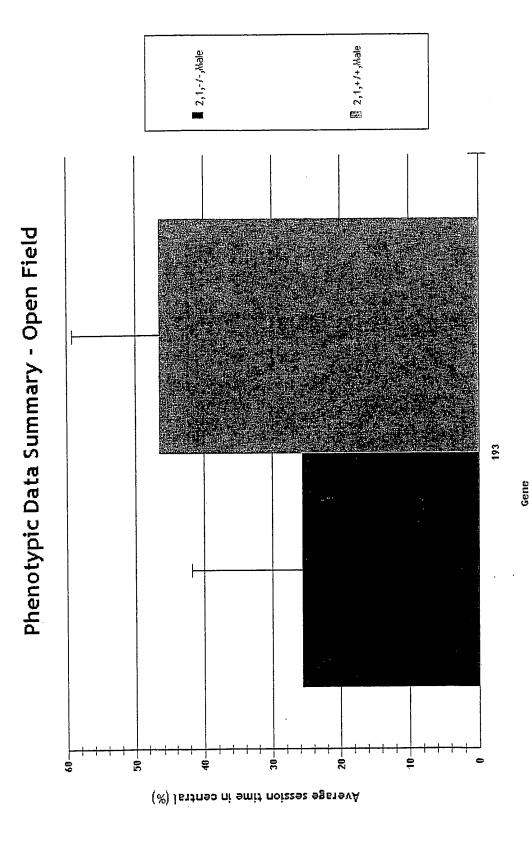


FIGURE 4

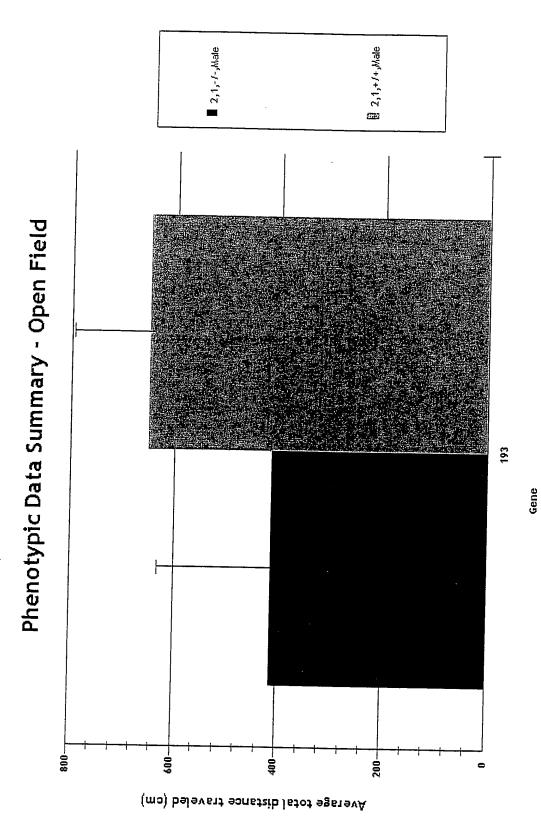


FIGURE 5